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The PARP family: insights into functional aspects of poly (ADP-ribose) polymerase-1 in cell growth and survival

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Abstract

PARP family members can be found spread across all domains and continue to be essential molecules from lower to higher eukaryotes. Poly (ADP-ribose) polymerase 1 (PARP-1), newly termed ADP-ribosyltransferase D-type 1 (ARTD1), is a ubiquitously expressed ADP-ribosyltransferase (ART) enzyme involved in key cellular processes such as DNA repair and cell death. This review assesses current developments in PARP-1 biology and activation signals for PARP-1, other than conventional DNA damage activation. Moreover, many essential functions of PARP-1 still remain elusive. PARP-1 is found to be involved in a myriad of cellular events *via* conservation of genomic integrity, chromatin dynamics and transcriptional regulation. This article briefly focuses on its other equally important overlooked functions during growth, metabolic regulation, spermatogenesis, embryogenesis, epigenetics and differentiation. Understanding the role of PARP-1, its multidimensional regulatory mechanisms in the cell and its dysregulation resulting in diseased states, will help in harnessing its true therapeutic potential.

1 | INTRODUCTION

Poly (ADP-ribose) polymerase (PARP) enzymes are a family of proteins involved in a number of cellular processes including gene regulation, chromatin remodelling, DNA repair and apoptosis.[1] These enzymes are present in all eukaryotes except yeast.[2] PARPs can either transfer a single unit of (ADP-ribose) or more than one (ADP-ribose) moieties from NAD^+onto substrates yielding poly (ADP-ribose) (PAR) chains, which can be of varying length and branch content. ADP-ribosyltransferase D-type 1 (ARTD-1 or PARP-1) falls in the latter category.[1,3] The PAR polymers are rapidly degraded by poly (ADP-ribose) glycohydrolase (PARG)[4] possessing both endoglycosidic and exoglycosidic activities,[5] and PAR hydrolase (ARH3), which also shares catalytic domain similarity with PARG.[6] However, ARH3 does not hydrolyse ADP-ribose-arginine, -cysteine, -diphthamide or -asparagine bonds.[6] Another set of enzymes known as macro domain-containing proteins and NUDIX hyrolases have also been reported to be involved in PAR degradation.[7,8] There are 17 different homologues of PARP that have a conserved catalytic domain with various domains like zinc finger, BRCT, SAM, SAP, ankyrin and macro domain.[9] Though PARP-1 has been demonstrated as a key player in DNA repair and cell death, many of its equally vital cellular functions have been overlooked. In this review, we discuss the distribution of PARP homologues across all organisms and the role of PARP-1 in various cellular functions like transcription, spermatogenesis, epigenetics and the most novel in differentiation and multicellularity.

2 | THE PARP FAMILY

Based on new proposed nomenclature by Hottiger et al.,[10] the human PARP (hPARP) family is classified into three groups depending on their motifs and functions: (1) PARP 1-5: have a conserved glutamate residue (Glu988); (2) PARP 6-8, 10-12 and 14-16: are putative mono-(ADP-ribose) polymerases and (3) PARP 9 and 13 which do not have PARP signature motif that binds NAD^+nor do they have Glu988 implying that they are inactive.[10] PARP superfamily can be subdivided into six clades which are shown in Table 1.

Out of 17 members, PARP-1 (113 kDa) was the first characterized and extensively studied enzyme recognized to play an essential role in DNA repair.[11] PARP-1 and PARP-2 share ~69% homology in the catalytic domain and they are documented as vital proteins in DNA repair system,[2] while PARP-3 is reported to be a mono-ADP-ribosylating enzyme by Loseva and group.[12] PARP-2 and PARP-3 were considered as a subgroup of PARP-1 as they all carry out synthesis of branched polymers.[13] PARP-4 also known as Vault PARP, is a ribonucleoprotein complex having PARylation activity and it is thought to be involved in multidrug resistance of tumour and intracellular transport.[14] Tankyrase-1 (TRF-1-interacting ankyrin-related ADP-ribose polymerase-1), also known as PARP5a, is identified to enhance telomere elongation by telomerase.[15] Other PARP homologues show structural and functional differences. Tankyrase-2 lacks N-terminal HPS (His-Pro-Ser) domain, but it may share some overlapping functions with tankyrase-1.[16] Other PARP family members like tiPARP, PARP-12 and PARP-13 share PARP catalytic, WWE and CX8CX5CX3-like zinc finger domains.[2] PARP-13 has been reported to be an important regulator of cellular mRNA via regulation of miRNA activity.[17] The next subgroup which includes PARP-9/BAL1, PARP-14/BAL2/CoaSt6 and PARP-15/BAL3 are macro-PARPs, characterized by macro domains positioned before the PARP domain. This domain is found to be involved in transcriptional repression and X-chromosome inactivation, suggesting it as a transcription factor.[18] The RNA recognition motif (RRM) and the Gly-rich domain of PARP-10 are known to help in binding of RNA with proto-oncoprotein c-Myc.[2] Other PARP family members such as PARP-6, PARP-8, PARP-11 and PARP-16 have been identified but their functions are still elusive, though PARP-8 and 16 have been recently shown to be involved in assembly or maintenance of membranous organelles.[19]

3 | DISTRIBUTION OF PARP ACROSS LIFE

3.1 | PARP in lower life forms

3.1.1 | PARP in bacteria

Numerous PARP-like proteins are detected in several bacterial genomes.[20,21] Till now, around 28 PARP homologues have been suggested across 27 bacterial species.[22] However, only a few bacteria possess the entire machinery required for PARP metabolism. Some also show the conserved histidine-tyrosine-glutamate (H-Y-E) catalytic triad which is essential for its activity.[21] PARP from *Herpetosiphon aurantiacus* has been reported to have conserved catalytic triad having the same characteristics as human PARP-1 enzyme.[21]

3.1.2 | PARP in archaea

Archaea do show the presence of PARP homologues. PARP-like thermozymes have been identified from *Sulfolobus solfataricus*. This PARP-like protein shows oligo (ADP-ribosyl) transferase activity and DNA-binding activity.[23]

3.1.3 | PARP in viruses

PARP-like proteins have also been identified in a few double-stranded DNA viruses [24] such as *Aeromonas* phage—Aeh1, *Anticarsia gemmatalis* nucleopolyhedro virus, invertebrate iridescent virus 6 and cellulophagaphage phi4:1. All these viral PARPs have been found to possess the conserved catalytic triad H-Y-E with an exception of one which has an aspartate instead of glutamate suggesting that these PARPs are active ADP-ribosyl transferases. Some viruses such as Herpes simplex virus and Epstein-Barr virus have also been reported to use PAR metabolism for their replication.[25,26]

3.2 | PARP in higher eukaryotes

PARPs are found in a divergent group of eukaryotes.[9,10] PARP expression has been identified in nearly all eukaryotic cells ranging from plants to vertebrates.[27] PARP-1 was long assumed to be the single enzyme with PARylation function until two PARP isoforms were discovered in plants.[28] Citarelli et al.[29] investigated at least two more PARP proteins in the last common extant ancestor of eukaryotes.

In conclusion, it is clear that the complexity of PARP proteins is augmented with the evolutionary level of the species. Vyas et al.[19] evidently illustrated that this domain complexity confers the diversity in functions to the PARP family.

PARP-1 is best studied out of this 17-member family of hPARPs. PARP has been implicated in development and cell differentiation from lower life forms to higher eukaryotes.[30] However, it is involved in a plethora of functions and many of its functions in spermatogenesis, epigenetics and differentiation remain unclear. Thus, understanding PARP-1 and its role in the above processes is the focus of this review.

4 | PARP-1: STRUCTURE, ACTIVATION SIGNALS AND ITS DIVERSE CELLULAR ROLES

4.1 | Gene organization of PARP-1 and its modifications

PARP-1 (EC 2.4.2.30) is a prominent member of the PARP family. It is a nuclear enzyme with approximately 10^6 molecules per cell [31] and accounts for 80%–90% of total cellular PARylation. Gene structure of PARP-1 mainly consists of DNA binding, an auto modification and a catalytic domain (Fig. 1). (1) The N-terminal DNA-binding domain has three zinc fingers and a nuclear localization sequence (NLS). The two homologous zinc finger proteins (Zn1 and Zn2) are characterized by a CCHC ligand pattern.[32,33] (2) The auto modification domain has BRCA1 C terminus (BRCT) motif and it is involved in protein-protein interaction.[2,10,34] (3) The catalytic domain at C terminus comprises of PARP signature motif (six β-strands and one α-helix) that binds to $NAD^+$and glutamate residue at its 988 position.[2]

TABLE 1 Distribution of PARP. PARP has been divided into six clades depending on the domains present[22,29] and [30]

Clade	Clade sub group	Class	Key features
Clade 1	Clade 1A	Amoebozoa (*Dictyostelium*) Opisthokonta (Fungi) Chromalveolates	Ankyrin repeats, WGR PRD, PARP catalytic domains.
	Clade 1B	Opisthokonta (animals and *Choanoflagellata*) and the Excavata (the *Heterolobosea* member Naegleria)	three N-terminal zinc fingers that contribute to DNA binding, a BRCT domain and a PADR1 domain in addition to WGR, PRD and the catalytic domain
	Clade 1C	Oomyocete Phytophtora species (within the Excavata) and one basal animal.	WGR, PRD and PARP catalytic domains and mostly do not contain other functional domains.
	Clade1D	Opisthokonta, the animals *Xenopus laevis* (Q566G1) and *Schistosoma japonicum* (Q5DAZ0) and the fungus *Batrachochytrium dendrobatidis* and Plantae (land plants) as well as ciliate members of the Chromalveolates.	WGR, PRD and PARP catalytic domains and mostly do not contain other functional domains.
	Clade 1E	most of the fungal members of Clade 1	BRCT domains N-terminal to WGR, PRD and PARP catalytic domains.
	Clade 1F	the Excavata	—
	Clade 1G	Opisthokonta (both animals and the Choanoflagellate *Monosiga brevicollis*)	only WGR, PRD and PARP catalytic domains
	Clade 1H	Two *Caenorhabditis elegans (C. elegans)* proteins	PADR1, WGR, PRD and PARP
Clade2	Clade 2A	—	an N-terminal WWE domain, the PARP signature and a C-terminal extension
	Clade 2B	—	only the PARP signature and the C-terminal extension
Clade 3	Clade 3A	—	RRM RNA-binding domain, a glycine-rich region (GRD), and a UIM domain
	Clade 3B	*Trichoplax adhaerens*	Macro domain N-terminal to their C-terminal catalytic domain
	Clade 3C	—	Macro domain N-terminal to their C-terminal catalytic domain
	Clade 3D	two *Dictyostelium discoideum* and four *Tetrahymena thermophila* proteins	—
	Clade 3E	—	one to two WWE domains, alone or in combination with zinc fingers (either CCCH or CCCH types) in front of their PARP catalytic domains
	Clade3F	—	PARP9
Clade 4	Clade 4	—	15–18 ankyrin repeats followed by a sterile alpha motif (SAM) and the PARP catalytic domain
Clade 5	Clade 5A	Opishthokonts (animals)	the PARP signature is found in the middle of the protein, rather than at the C terminus
	Clade 5B	Amoebozoa	—
Clade 6	Clade 6A	Opisthokonts (animals and fungi), Excavates (Parabasalids and Heterolobosa), and Plantae (chlorophyta and bryophytes)	N termini with no known functional domains and C-terminal extensions beyond the PARP catalytic domain of varying lengths
	Clade 6B		PfamB_2311 domains as well as the PARP catalytic domain
	Clade 6C		PfamB_2311 domain and a PARP catalytic domain
	Clade 6D	Deuterostomes with the exception of the mollusc *Lottia gigantean*	PfamB_2311 domain and the PARP catalytic domain
	Clade 6E	seven proteins encoded by *Trichomonas vaginalis*	PfamB_2311 domain and the PARP catalytic domain

The next important component of this enzyme is the PARP signature motif (PSM). It has two sites, acceptor site for adenosine and donor site for nicotinamide wherein ADP residues from $NAD^+$are transferred to target site.[35] His-862 and Glu-988 play important role in NAD^+binding.[36] In addition to this, WGR domain also contains highly conserved amino acid sequence i.e. Trp, Gly and Arg, but its role

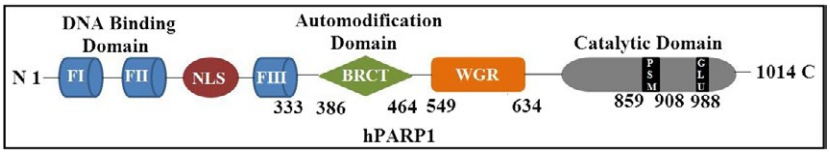

FIGURE 1 **Structural organization of human PARP-1 (hPARP-1):** It is characterized by FI, FII: Zinc finger motifs, FIII: Zinc ribbon domain (1-333 aa); NLS: Nuclear localization sequence; BRCT: BRCA1 C terminal motif (386-464 aa); WGR domain (549-634 aa) and the most conserved catalytic domain with PARP signature motif (PSM) between 859-908 aa and Glutamate (Glu) at 988 position.

TABLE 2 Post-translational Modifications of Poly (ADP-ribose) polymerase 1

Modification in PARP-1	Source	Residue modified	Activator	Result	References
Auto modification Poly (ADP-ribosylation)	PARP	K498, K521 and K524	Intact and damaged DNA	Regulation of PARP activity	Altmeyer et al.[38]
Mono-ADP-ribosylation	SIRT6	K521	dsDNA damage	Enhances double-strand break repair under oxidative stress	Mao et al.[42]
Sumolyation small ubiquitin-related modifier (SUMO)	SUMO-2 SUMO 3	K203, K486 and K512	Heat shock intact DNA	Transcriptional co-activator of hypoxia-responsive genes and promotes induction of the heat shock-induced HSP70.1 promoter	Zilio et al.[43]
Acetylation	p300/CREB-binding protein	K498, K505, K508, K521 and K524	Inflammatory stimuli	NF-κB-dependent gene activation	Hassa et al.[40]
Phosphorylation	ERK1/2 Protein Kinase C	S372 and T373	DNA damage	Neuronal cell death Decreased PARP-1 DNA-binding and catalytic activity	Kauppinen et al.,[41] Beckert et al.[39]

is yet to be identified.[2,34] However, Langelier et al.[37] showed that Zn3 along with Zn1 and WGR domain of PARP-1 together bind to the DNA damage leading to structural changes eventually abridging DNA damage site to its catalytic domain.

Other than auto modification by PARylation, PARP-1 itself undergoes various other modifications enlisted in Table 2 that has various cellular effects.[38–43]

4.2 | Mechanism of PARP-1 activation

The enzymatic activity of PARP-1 is stimulated significantly in the presence of a range of activators like damaged DNA, non-B-DNA structures, nucleosomes and various protein-binding partners.[1,44–46] Lonskaya et al.[47] reported that DNA bent, cruciform DNA or stably unpaired DNA regions can also stimulate PARylation. The activation signal for PARP-1 is DNA damage although several reports illustrate that PARP-1 may also be activated in the absence of DNA damage. The best characterized ligands for PARP-1 are single-strand and double-strand breaks (SSBs and DSBs).

There are reports suggesting that PARP-1 activation by SSBs requires presence of both the zinc fingers while only Zn1 is required for DSBs.[33] Zn1 has been demonstrated to relay the signals to the catalytic domain for formation of PAR molecules,[33,48] while Zn2 has been shown to be majorly involved in DNA binding as compared to Zn1 due to its higher affinity to DNA.[49] Eustermann et al.[50] have demonstrated very recently how the two zinc fingers recognize SSBs and coordinate domain folding in PARP-1 to control the activity of the C-terminal catalytic domain. PARP-1 has been reported to have affinity for intact DNA structures and recognizes specific octamer motif "RNNWCAAA" found in various gene promoters.[51]

Another mode of alternative DNA-independent mode of PARP-1 activation is based on kinase cascades. Phosphorylated ERK2 has been shown to significantly enhance and maximize PARP-1 catalytic activity in the presence and absence of damaged DNA.[41,52] Interaction between PARP-1 and a pre-phosphorylated kinase has also been shown to mediate PARP-1 activation.[52,53] Likewise, phosphorylation by activated calcium-dependent protein kinase (CaMKII) is also capable of activating PARP-1 enzyme during neuronal development thereby promoting the nuclear export of its negative regulator KIF4.[54] Moreover, overexpression of protein phosphatase 5 (PP5) led to increase in PARP-1 enzymatic activity in response to double-stranded DNA breaks.[55] Nuclear nicotinamide mononucleotide adenylyl transferase 1 (NMNAT1), an enzyme involved in NAD^+synthesis, also associates with PAR to enhance PARP-1 enzyme activity.[56] Other proteins regulating PARP-1 activity include Ku,[55] histone variant macroH2A1.1[57] and KIF4.[58] Protein-protein interactions also seem to activate PARP-1. Mao et al.[42] have demonstrated that SIRT6 activates PARP-1 by mono-ADP-ribosylating it in position Lys521. Developmental or environmental stimuli induce PARP-1 activation and the PAR-dependent nucleosome loosening leading to histone stripping and hence opening of the chromatin structure. This process allows

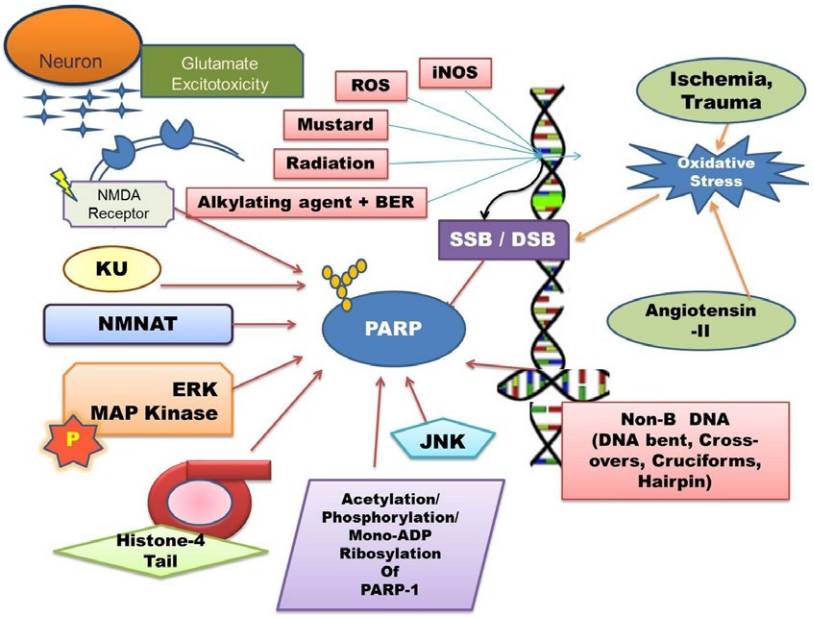

FIGURE 2 Mechanism of PARP-1 Activation. The nuclear enzyme PARP-1 can bind to DNA breaks resulting in the activation of the enzyme. DNA breaks are caused either by ROS, RNS or radiation or indirectly by DNA repair machinery where breaks are introduced into the DNA strands as in the case of alkylating DNA damage. Binding to special non-B-DNA structures such as bent or cruciform DNA or four-way junctions may culminate into PARP-1 activation. Protein-protein interactions or covalent modifications (e.g. mono-ADP-ribosylation, acetylation or phosphorylation) have also been described as activation mechanisms for PARP-1 which are DNA-independent. Other proteins activating PARP include nuclear NMNAT, Ku and phosphorylated ERK2 and Histone-4 tail

transcriptional activation. This PAR-mediated chromatin loosening phenomenon is detected at larval salivary-gland polytene chromosome puffs.[59] Hence, PARP-1 can be activated by DNA-dependent and -independent manner which is summarized in Fig. 2.

4.3 | PARP-1: single protein with varied roles

4.3.1 | PARP-1 in DNA repair

ADP-ribosylation activity of PARP-1 is an instantaneous biochemical response to DNA damage induced by ionizing radiations, alkylations etc. At low levels of DNA damage, it detects DNA damage followed by repair and cell survival, whereas at high levels of DNA damage, it activates the cell death pathway.[60] Upon DNA damage, PARP-1's zinc finger FI/Zn1, FII/Zn2 and FIII/Zn3 motifs have been reported to relay binding signal to catalytic domain followed by the recruitment of proteins involved in repair mechanism such as base excision repair (BER), single-strand breaks (SSBs) and double-strand breaks (DSBs) repair.[1,61] It is also indicated to act as a DNA damage sensor [62] and help in chromatin remodelling at DNA damage sites.[63] A variety of proteins like ALC1, histone mH2A1.1, scaffold attachment factor SAFB1 have been illustrated to be recruited to DNA damage sites via PARP-1 thus proving its indispensable role in DNA repair.[64–66] Evidences show presence of PAR-binding zinc finger motifs in DNA damage response and checkpoint regulation proteins.[67,68] PARP-2 was also shown to be involved in the later steps of BER/single-strand break repair.[69] In nucleotide excision repair, PARP-1 inhibition or depletion has also shown to cause low efficiency of removal of UV-induced DNA damage.[70] Among mammalian DNA repair pathways, PARP-1 has been also implicated in homologous recombination[71] and non-homologous end-joining pathways.[72] PARP-1 has been reported to interact with replication fork protein (Timeless) in a PAR-independent manner thereby allowing its recruitment to DSB sites to promote homologous recombination.[73] Thus, it is clearly illustrated that PARP-1 plays a vital role in DNA damage response.

4.3.2 | PARP-1 in cell death

Under normal physiological conditions, cell morphology, numbers, pattern and injury are taken care of by the process of apoptosis.[74] The mode of cell death depends on the extent of DNA damage. Low DNA damage can activate PARP-1 resulting in cell survival via DNA repair mechanisms. At moderate levels of DNA damage, cell undergoes apoptosis and PARP-1 activation results into cleavage of PARP-1 by caspases-3 and -7 into two fragments (89 kDa and 24 kDa)[75] which is believed to be a key feature of apoptosis.[76] N-terminal 24 kDa fragment remains in nucleolus and other 89 kDa fragment translocates from nucleus to cytosol wherein it acts as a target for autoimmunity.[77] Severe DNA damage leads to programmed necrotic cell death through over-activation of PARP-1.[78] Ring finger protein 146 (RNF146), a cytoplasmic E3-ubiquitin ligase, acts as a direct interactor of PARP-1 during this process and elicits release of PARP-1 from the nucleus. This has been demonstrated during myocardial ischaemia-reperfusion injury.[79] On the other side, in caspase-independent cell death, it plays an important role in the release of apoptosis-inducing factor (AIF) from mitochondria to nucleus. Yu et al.[80] have studied the dependence of PARP-1 and AIF in caspase-independent cell death which is termed as 'parthanatos'. PARP-1 has been reported to play a very crucial role in initiation and regulation of this type of cell death.[81] Parthanatos has been detected in many disease conditions like stroke, Parkinsons, diabetes, etc.[82] Upon PARP-1 activation stimulated with various DNA-damaging agents like NMDA, H_2O_2, etc., AIF translocates from mitochondria to nucleus and finally culminates into cell death.[83–85] On the contrary, Mir et al. showed that staurosporine-induced cell death did not involve PARP.[86]

PARP-1 is also reported to be involved in autophagy induced by DNA damage.[87] PARP-1 via autophagy displays a cytoprotective role in oxidative stress-induced necrotic cell death.[88] Moreover, Son et al.[89] have also reported that cadmium-mediated ROS generation leads to PARP-1 activation and energy (ATP) reduction, eventually culminating into autophagy in skin epidermal cells. Wyrsch et al.[90] have found that PARP-1 and PARP-2 control cytosolic Ca^{2+}shifts from extracellular and intracellular sources during oxidative stress. The different Ca^{2+}signals arise from the transient receptor potential melastatin 2 (TRPM2) channels located in the cellular and lysosomal membranes. This Ca^{2+}overload induces specific stress kinase response which leads to autophagy or cell death. Under mild oxidative stress conditions, PARP-1 operates as an autophagy suppressor after oxidative stress leading to cell death by activating downstream of extracellular signal-regulated kinase 1/2 (ERK1/2) and AKT. Under severe oxidative conditions, PARP-2 induces Ca^{2+}shifts from lysosomes, while PARP-1 becomes completely inactive. The cytosolic Ca^{2+}overload leads to phosphorylation of p38, stress-activated protein kinase/Jun amino-terminal kinase (SAPK/JNK), and cyclic AMP response element-binding protein (CREB) with its activating transcription factor (ATF-1), further activating autophagy markers leading to cell survival.

PARP-1 and related PARP family members are at the intersection of conversing stress signalling pathways. Oxidative stress causes disruption in redox potential that extends to the ER, causing accumulation of misfolded proteins, finally stimulating the unfolded protein response (UPR).[91] It would be interesting to know if PARP-1 has a role in ER stress-mediated cell death as it is upstream to autophagy, where PARP-1 is demonstrated to play an essential role. Hence, it is clear that PARP-1 is an essential regulator in many of the cell death pathways and this has been demonstrated in many tissues. However, a very interesting work by Jog and Caricchio[92] illustrates a characteristic difference in PARP-1-mediated necrosis in males and females. Male mice were shown to be prone to PARP-1-mediated necrosis while female mice showed PARP-1-independent cell death.[92] Understanding the role of PARP-1 in different stress conditions and even in different sexes would help us dissect out pathomechanisms of various disease conditions.

4.3.3 | PARP-1 and epigenetics

The poly (ADP-ribosyl)ation of histones leading to open chromatin conformation at DNA damage sites was the first indication to the function of PAR as an epigenetic modification.[2] Recent evidence has shown that PAR has an important role in the epigenetic regulation of chromatin structure and in gene expression under physiological conditions wherein DNA integrity is maintained.[93] Lodhi et al.[94] have demonstrated PARP-1 as a genome-wide epigenetic memory mark in mitotic chromatin. They report that PARP-1 establishes stable epigenetic marks at the transcription start sites in metaphase chromatin and these marks are a prerequisite for transcriptional restart after mitosis. Moreover, PARP-1 activity epigenetically regulates mitochondrial DNA repair and transcription.[95] PARP-1 also associates with genome-wide epigenetic regulatory elements suggesting a functional interplay between PARP-1 and DNA methylation.[96] Previous studies have shown that PARP-1 can affect the genomic DNA methylation pattern via DNA methyl transferase, Dnmt1, both by regulating its expression as well as activity.[93,97] Furthermore, the role of PARP-1 in DNA methylation events has been explored in induced pluripotent stem cells (iPSCs).[98] Recently, PARP-1 has been shown to be associated epigenetically with Tet2 (a methyl cytosine dioxygenase) during somatic cell reprogramming which leads to transcriptional induction at the pluripotency loci.[99] PARP-1 has also been demonstrated to interact with TIP5 via non-coding RNA, thereby playing a role in maintenance of silent rDNA chromatin in mid-late S phase.[100] Though, these studies suggest the possible epigenetic involvement of PARP-1; its mechanistic role in epigenetic control is still elusive and remains to be an area of great interest to researchers.

4.3.4 | PARP-1 as a chromatin modulator

Chromatin consists of genomic DNA, linker histones (H1), core histones (H2A, H2B, H3 and H4) and other chromatin-associated proteins. Early reports have shown that purified PARP-1 could ADP-ribosylate chromatin proteins (e.g. mainly H1), by decondensation of chromatin and destabilization of nucleosomes.[101] Also proven in recent reports, PARP-1 binding to chromatin can change the conformation and composition of nucleosome.[32,102] In addition, it has also been demonstrated that PARP-1 interacts with core histone variants resulting in the recruitment and integration of histone variants to specific sites in the genome.[57] Local chromatin loosening by PARP-1 has also been demonstrated well at the puff loci in *Drosophila* facilitating transcription and eventually helping chromatin remodelling during development.[59] Nalabothula et al.[96] discussed the possible mechanisms of chromatin structure remodelling by PARP-1 as: a) it binds between entry and exit sites between nucleosomes and linker DNA, b) it PARylates histones, linker histone H1, etc. thus modifying chromatin architecture and c) it competes with histone H1 for nucleosome binding. All the above reports strengthen the role of PARP-1 in chromatin remodelling.

4.3.5 | PARP-1 in transcription

It is well studied that PARP-1 behaves as chromatin modifier at transcriptional level with a number of in vitro and in vivo experiments. Electrostatic repulsion between DNA and histones due to transfer of negatively charged PAR molecules onto accepter proteins promotes transcription by recruiting transcriptional machinery.[103] PARP-1 is observed to be more localized at the promoter regions of most actively transcribed genes.[104] The transcriptional regulatory roles of PARP-1 are manifested mainly through two processes, modulating chromatin structure and acting as a part of enhancer/promoter-binding complexes. Based on the cell type, it can enhance transcription with co-activators or inhibit transcription by repressors.[105] Chromatin-dependent gene expression is controlled by

PARP-1 interacting with histones at promoter.[104] The type of histone modification (acetylation, phosphorylation and methylation) is very essential for interaction between PARP-1 and DNA because it can add structural changes into histones.[106] Phosphorylation of histone variant, H2Av, promotes activity of PARP-1 in *Drosophila* at specific promoter regions.[107] PARP-1 is also found to be localized at DNA repair sites after binding to other histone variant, macroH2A.[108] Also, macroH2A1-stimulated H2B acetylation was seen in cancer progression which was PARP-1-dependent.[109] Depletion of PARP-1 activity resulted into ineffective loading of RNA polymerase II transcriptional machinery implying its role in gene regulation.[110]

Recent studies suggest that PARP-1 functions as a co-activator, which upregulates the transcription of Nrf2, promoting the interaction among Nrf2 and ARE (antioxidant response elements).[111] Reduced expression of CCN2 was found in tubular epithelial cells of kidney upon knockdown of PARP-1.[112] In addition to this, PARP-1 also functions as an insulator that organizes the genome into distinct regulatory units by controlling the effects of enhancers on promoters, or by preventing the spread of heterochromatin.[113] In vivo and in vitro binding studies of PARP-1 and transcription factor Yin Yang 1 (YY1) suggested that PARP-1 plays a promoter regulatory role and inhibits the transcription of Cxcl12. In addition, changes in PARP-1-CTCF interactions due to serum shock induced recruitment of circadian loci to the lamina leading to transcriptional attenuation.[114] PARP-1 is also known to be acting as an exchange factor thereby controlling transcription. Recently, it has been demonstrated that PARP-1 functions in remodelling of promoter-associated nucleosomes by replacing H2A.Z by H2A from *FOS* promoter to allow transcriptional activation in response to ERK signalling.[115] Thus, the underlying mechanism of PARP-1-mediated transcriptional regulation is very complex and extensive and hence more studies are required to explore the transcriptional role of PARP-1.

4.3.6 | PARP and spermatogenesis

Both PARP-1 and PARP-2 have been found to have a significant role in spermatogenesis.[116] It has been observed that there is significant PARP expression during the earlier stages of spermatogenesis and its transcription declines during late stages of maturation.[117,118] The levels of PARP-1, PARP-2 and PARP-9 were found to be increased in mature sperms as compared to immature sperms [116] and interestingly PARP-1 was also found to be downregulated during the haploid stage of meiosis.[119] The presence of PARG in the nuclei of rat primary spermatocytes also suggests that the levels of poly (ADP-ribose) in these germ cells are highly regulated.[117] Moreover, Meyer-Ficca et al.[120] reported the presence of PAR polymerization by PARP-1 and PARP-2 in rat spermatids, highest during the phase of chromatin condensation.

Studies demonstrating an increase in DNA strand breaks in all population of elongating spermatids in human testis [121] and the presence of higher levels of PARP-1, PARP-2 and PARP-9 in ejaculated sperm from fertile men compared to infertile men indicate a possible relationship between PARP expression and male infertility.

4.3.7 | PARP-1 in cell differentiation/multicellularity

Out of the various roles of PARP-1, its role in cell differentiation and multicellularity has yet to be unravelled. However, accumulating reports in different model systems suggest a definite role of PARP-1 in growth and multicellularity. For example, Drosophila PARP has been shown to act in ectodermal specification and neural crest development in zebrafish.[122] Our laboratory studies are indicative of PARP's role in *D.discoideum* development wherein its downregulation led to arrested development.[123] Recent studies from our laboratory show PARP-1 involvement in *D. discoideum* growth and multicellularity by ADPRT1A (PARP-1 orthologue) overexpression which led to delayed growth and developmental morphogenesis.[124] We have also reported that PARP may be essential in combating stress conditions in *D. discoideum*.[83–85,125,126] Genetic studies on PARP-1 orthologues in fungus demonstrated defective development and decreased life span.[127–129] As we move to the higher life forms like plants, it was seen that AtPARP-1 and/or AtPARP2 knockdown reported to alter *Arabidopsis* development [130] and AtPARP2 orthologue in oilseed rape (*Brassica napus*) did not affect its development.[131] However, further work is mandatory to explore the role of PARP in plant development. In addition, studies in Drosophila also suggest importance of PARP in chromatin loosening at ecdysone-inducible regions thereby inducing purparium formation and metamorphosis.[59,132] These results are also substantiated by mice studies wherein PARP-1 and PARP-2 double-mutant mice were found to be not viable and die at the onset of gastrulation, establishing the importance of both the PARPs during early embryogenesis.[133] Recently, Hamazaki et al.[134] have shown that PARP inhibition caused inhibition of DNA demethylation of the *IL17d* promoter region at the two-cell stage leading to downregulation of genes essential for early embryogenesis. Thus it is clear from the above that a strong association of PARP-1 exists in differentiation and multicellularity, which is yet to be explored in detail.

4.3.8 | PARP-1 in metabolic regulation

PARP-1 has been known for its role in DNA repair as discussed in above sections. However, recent data suggest a role for PARP-1 in metabolic regulation by influencing mitochondrial function and oxidative metabolism. Mouse knockout studies showed that PARP-1 deletion led to increased food intake.[135,136] PARP-$1^{-/-}$ mice showed an increased metabolic rate.[137] PARP-1 has also been associated with reduction in the glycolytic rate which has been linked to a reduction in NAD^{+}availability over the years.[138] Over-activation of PARP activity can lead to metabolic perturbations through reduction in ATP, NAD^{+}/NADH levels, which is enough to impair carbohydrate metabolism.[139] It also changes the flow of glycolytic metabolites into Krebs cycle and thereby compromised energy production in mitochondria.[140] However, recent evidence indicates that PARP-1 may be responsible for reduction in hexokinase activity and hence affects the

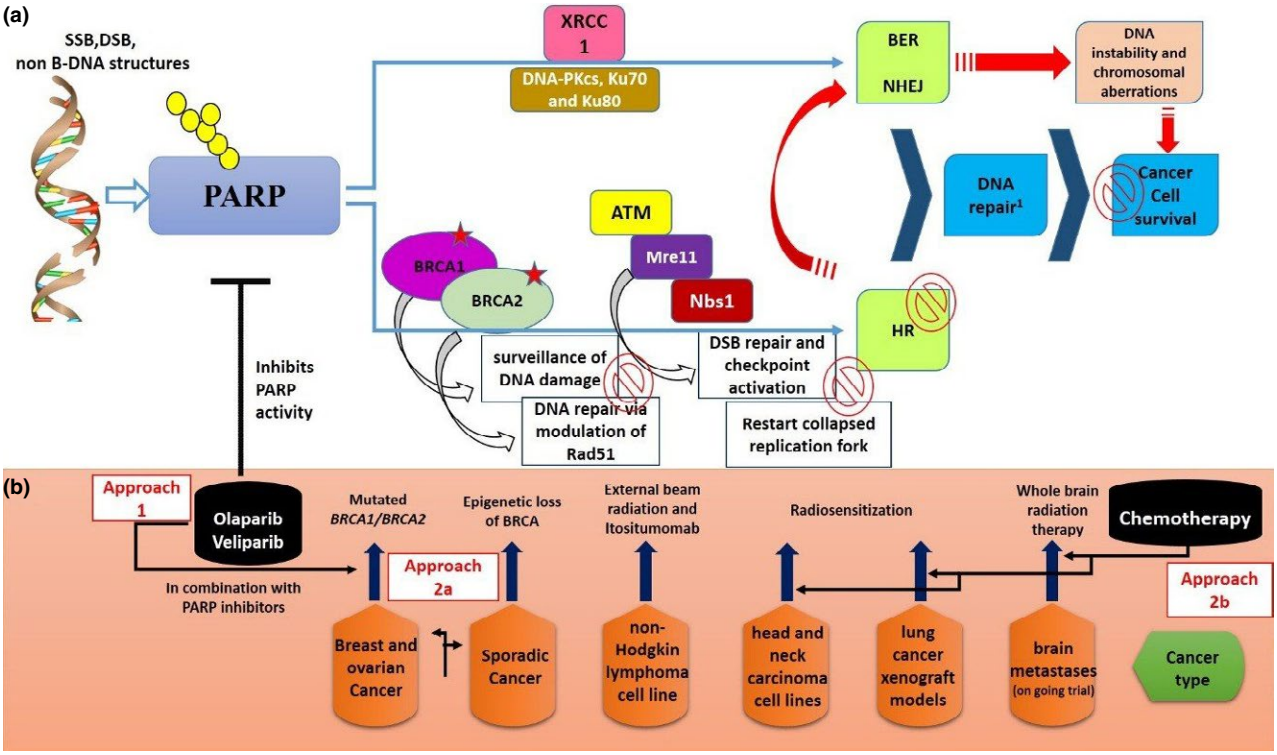

FIGURE 3 PARP-1 and cancer therapy. (a) In normal cells, upon DNA damage like SSB, DSB and non-B-DNA structures, PARP-1 gets activated and thereby aids in the recruitment of DNA repair proteins such as the scaffolding protein XRCC1 to sites of SSBs through BER, whereas DNA-PKcs, Ku70 and Ku80 to sites of DSBs through NHEJ. It also aids HR via recruitment of factors like ATM, Mre11 and Nbs1 to sites of DSBs. Another very essential process of HR repair involves localization of BRCA-1 and BRCA-2 to sites of double-stranded DNA damage. In cancer cells bearing BRCA1/2 mutations or deficiency (red star), cells are rendered faulty in HR repair (red no symbol) and thus there is complete dependence on NHEJ (error-prone) for DSB DNA repair and SSB for BER (red arrows); both of which are PARP-1-dependent. Thus, PARP inhibition serves as an excellent approach for therapy. BRCA1/2 mutations or deficiency along with PARP-1 inhibition leads to amplification of DNA instability due to impairment in BER-, NHEJ- and ATM-mediated HR repair and chromosomal aberrations results in cell death. (b) PARP-1 inhibitors like Olaparib, Veliparib, etc. have been promising therapeutic candidates in case of breast cancer and ovarian cancer—Approach 1. Approach 2a uses PARP-1 inhibitors in case of epigenetic modulation or artificial inactivation of BRCA pathway in case of sporadic cancers, whereas approach 2b involves use of chemotherapy and radiation along with PARP-1 inhibitor depending on the cancer type

cellular glycolytic rate via poly (ADP-ribosyl)ation of hexokinase directly.[141] PARP-1 and PARP-2 activation have also been demonstrated to affect mitochondrial activity negatively.[142] Hence, PARP inhibition arises as therapeutant to treat mitochondrial dysfunction.

In addition, PARP-1 also plays a crucial role in the circadian entrainment and regulates feeding behaviour. Asher et al.[143] demonstrated that CLOCK (Circadian transcription factor)–BMAL1-dependent gene expression was altered in PARP-1-knockout mice, in response to changes in feeding times. In contrast, the deletion of PARP-2 did not affect food intake or daily behaviour.[135] Moreover, both PARP-1$^{-/-}$ and PARP-2$^{-/-}$ mice displayed enhanced energy expenditure.[135,138] PARP-1$^{-/-}$ mice showed an increased mitochondrial content in their brown adipose tissue (BAT),[138] which physiologically renders them to be able to maintain their body temperature during cold exposure. Interestingly, PARP-2 deletion does not influence mitochondrial biogenesis in BAT.[138] Furthermore, it has been suggested that PARP-1 acts as a positive regulator of adipogenesis and adipocyte function resulting in fat deposition.[144] Studies have confirmed that PARP-1 regulates adipogenic gene expression and is required selectively for adipocyte function.[145] PARP-1$^{-/-}$ and PARP-2$^{-/-}$ mice also displayed an increased glucose clearance [135,138] suggesting the increased insulin sensitivity. Thus, these reports suggest the metabolic involvement of PARP-1 and PARP-2; however, more studies are needed to confirm these findings and to explore new metabolic regulatory functions of PARP.

4.3.9 | PARP-1 and cancer

Errors in replication process, production of ROS and UV radiations result in DNA damage which includes single-strand breaks (SSBs), double-strand breaks (DSBs), etc. Cells then signal DNA repair pathways such as nucleic acid excision repair (NER), base excision repair (BER), mismatch repair (MMR), non-homologous end-joining (NHEJ) and homologous recombination (HR) resulting into cell survival with an exception of tumour cells. PARP-1 and PARP-2 are key regulators for the function of DNA repair mechanisms; however, genetic disorders, such as BRCA1 and BRCA2 mutations, prevent

TABLE 3 PARP inhibitors—Olaparib and Veliparib in various disorders

Mode of administration	Disease/disorder	Nature of disorder	Clinical trial status and results	Dosage (mg)	Side effects/toxicity	Reference
(a) PARP inhibitor Olaparib in various cancers						
Oral, monotherapy	Ovarian cancer	Recurrent; with *BRCA1* or *BRCA2* mutation	Phase II; positive	200; Twice a day	Anaemia and Vomiting	Kaye et al.,[167] Mateo et al.[168]
				300; Twice a day	Anaemia	Mateo et al.[168]
				400; Twice a day	Fatigue, nausea, vomiting and decreased appetite	Gelmon et al.,[169] Kaye et al.,[167] Ledermann et al.,[170] Kaufman et al.[171]
		Advanced; without *BRCA1/2* mutation	Phase II; negative	400; Twice a day	—	Gelmon et al.[169]
	Triple-negative breast cancer	Advanced; with *BRCA1* or *BRCA2* mutation	Phase II; positive	100; Twice a day	Fatigue and nausea	Tutt et al.[172]
	Breast cancer	Advanced; with *BRCA1* or *BRCA2* mutation	Phase II; positive	400; Twice a day	Fatigue, nausea and vomiting	Tutt et al.[172]
Oral, Combination therapy with Cediranib	Ovarian cancer	Recurrent; with *BRCA1* or *BRCA2* mutation	Phase I; positive	200/400 mg twice daily plus Cediranib 30 mg daily	Bowel obstruction, fatigue, hypertension, thrombocytopenia	Liu et al.[173]
Oral, Combination therapy with Cediranib	Ovarian fallopian tube, or primary peritoneal cancer	Recurrent; platinum-sensitive, or with *BRCA1/2* mutations	Phase II; Positive compared to monotherapy (400 mg)	200 mg twice daily plus Cediranib 30 mg daily vs 400 mg Olaparib	Fatigue, diarrhoea and hypertension	Liu et al.[174]
Oral, Combination therapy with Cediranib	Triple-negative breast cancer	Metastatic	Phase I; Negative	200/400 mg twice daily plus Cediranib 30 mg daily	—	Liu et al.[173]
Oral, Triple combination therapy with carboplatin and paclitaxel	Ovarian cancer	Advanced, with or w/o *BRCA1* or *BRCA2 mutations*, relapsed	Phase Ib/II; Positive	200 mg twice daily plus carboplatin and paclitaxel, followed by olaparib 400 mg	Neutropenia and anaemia	Oza et al.,[175] Rivkin et al.[176]
Oral, Triple combination therapy with carboplatin+paclitaxel and Chemo therapy	Ovarian cancer	Advanced, with or without *BRCA1* or *BRCA2 mutations*, relapsed	Phase I; Positive	200 mg twice daily plus carboplatin and paclitaxel, followed by olaparib 400 mg	Alopecia, nausea, neutropenia, diarrhoea, headache, peripheral neuropathy and dyspepsia	Oza et al.[175]
Oral; with Chemo therapy	Ewing sarcoma	Refractory	Phase II; Negative	400; Twice a day	Anaemia and thrombocytopenia	Choy et al.[177]
Oral, monotherapy	Pancreatic cancer	With germline BRCA1/2 mutation	Phase II; Positive	400; Twice a day	Fatigue, nausea, anaemia and vomiting	Kaufman et al.[171]
Oral, monotherapy	Prostate cancer	With germline BRCA1/2 mutation	Phase II; Positive	400; Twice a day	Fatigue, nausea, anaemia and vomiting	Kaufman et al.[171]
Intravenous; Combined with cetuximab (cet) and intensity modulated radiation therapy	Head and neck squamous cell carcinoma	Heavy smokers, locally advanced	Phase I; Uncertain/ ongoing	400 mg/m^2+cet 250 mg/ m^2 IV.	Mucositis, dermatitis, clinically insignificant lymphopenia, and hypomagnesaemia	Waxweiler et al.[178]

TABLE 3 (continued)

Mode of administration	Disease/disorder	Nature of disorder	Clinical trial status and results	Dosage (mg)	Side effects/toxicity	Reference
Oral; with temozolomide	Glioblastoma	Relapsed	Phase I; Positive penetration	400	—	Chalmers et al.[179]
Oral; with topotecan	Advanced solid tumours	—	Phase I; Negative	100 mg twice daily	— events	Samol et al.[180]
(b) PARP inhibitor Veliparib in various cancers						
Oral, monotherapy	Epithelial ovarian cancer	Recurrent or persistent; With germline BRCA1/2 mutation	Phase II; Negative; discontinued	400	Grade 3-fatigue, nausea, leukopenia, neutropenia, dehydration, and ALT. Grade 2 events-nausea, fatigue, vomiting and anaemia	Coleman et al.[181]
Oral; monotherapy	Serous ovarian cancer	Without BRCA1/2 mutation	Phase I; Negative	400	Nausea/vomiting, fatigue and leukopenia	Pahuja et al.[182]
Oral; monotherapy	Triple-negative breast cancer	Without BRCA1/2 mutation	Phase I; Negative	400	—	Pahuja et al.[182]
Oral; monotherapy	Castration-resistant prostate cancer	BRCA2-mutated metastatic	Phase I; Positive	400	—	Pahuja et al.[182]
Oral; with irinotecan	Triple-negative breast cancer	Without BRCA1/2 mutation With BRCA1/2 mutation	Phase I; Negative Phase I; positive	40 mg+irinotecan 100 mg/m^2	Leukopenia, neutropenia, nausea, diarrhoea, fatigue, anaemia and vomiting	LoRusso et al.[183]
Oral; Combined with Cisplatin and etoposide	Small cell lung cancer	Previously untreated	Phase I; positive	100+Cisplatin 75 mg/m^2+etoposide 100 mg/m^2	Dehydration, diarrhoea, fatigue, febrile neutropenia, heart failure, leukopenia, lymphopenia, nausea, neutropenia, respiratory failure and thrombocytopenia	Owonikoko et al.[184]
Oral, Combined with carboplatin and paclitaxel	Squamous (Sq) non-small cell lung cancer	Untreated advanced/metastatic	Phase III;	120 mg+carboplatin AUC 6 mg/mL/m IV and paclitaxel 200 mg/m^2 IV	—	McKee et al.[185]
Oral; with metronomic Cyclophosphamide	Solid tumours and lymphomas	Advanced	Phase I; Positive	60 mg+cyclophosphamide 50 mg	—	Kummar et al.[186]
Oral; with cisplatin and gemcitabine	Pancreas adenocarcinoma	Potential BRCA/PABL2 mutated	Phase Ib; Positive	80 mg+C 25 mg/m^2 IV, G 600 mg/m^2 IV	Anaemia, neutropenia, thrombocytopenia, haematologic toxicity and fatigue	O'Reilly et al.[187]
Oral; With Temozolomide (TMZ)	Castration-resistant prostate cancer	Docetaxel-pretreated patients with metastatic	Phase I; positive	40 mg+TMZ 150 mg/m^2	Thrombocytopenia, anaemia, fatigue, neutropenia, nausea and constipation	Hussain et al.[188]

DNA repair mechanism and increase the risk of malignancies.[146] Inhibition of DNA repair process may lead to cell death and this brings PARP-1 as a perfect target for anti-cancer therapy. PARylation of targeted proteins by PARP-1 on activation by SSBs and DSBs facilitates the recruitment of DNA repair proteins such as XRCC1 to sites of damage.[147,148] PARP-1 may also facilitate HR via recruitment of factors like ataxia telangiectasia-mutated (ATM, Ataxia Telangiectasia Mutated), Nijmegen breakage syndrome 1 (Nbs1) and mitotic recombination 11 (Mre11) to sites of DSBs.[149] However, major role in HR repair involves localization of BRCA-1 and BRCA-2. BRCA-1 plays an essential role in the surveillance of DNA damage and transduction of DNA repair responses, while BRCA-2 is directly involved in double-stranded DNA repair, *via* modulation of Rad51 by HR.[150]

PARP-1 inhibition does not cause cell lethality by itself, as the cell has an intact HR pathway for DNA repair. Cells that have a mutated *BRCA1* or *BRCA2* genes as in the case of breast cancer or those that are deficient in BRCA1 or BRCA2 proteins like sporadic cancers are found to be defective in their ability to repair DNA through HR and henceforth depend on error-prone NHEJ. This results in amplification of DNA instability and chromosomal aberrations eventually causing cell death (Fig. 3a). This synergistic effect has been very well demonstrated by Arun et al.,[151] wherein PARPi AZD2281 showed more promising results in BRCA1- and BRCA2-bearing mutants *via* induction of autophagy. This concept of synthetic lethality has been implemented upon in cancer therapeutics. In cases of breast and ovarian cancer, treatment with PARP-1 inhibitors Olaparib and Veliparib (Approach A) has found positive clinical results.[152] Epigenetic modulation or artificial inactivation of BRCA pathway (Approach 2a) in cases of sporadic cancer along with the use of PARPi plays a key to therapeutics. This synergistic inhibition of DNA repair poses as a double-hit mechanism for cancer cell death. PARPi can also be used in combination with chemotherapy and radiation (Approach 2b) to render the cells prone to cell death under enhanced damaged conditions as in cases of non-Hodgkin lymphoma cell line, use of PARPi in combination with both external beam radiation and ^{131}I-tositumomab; radio sensitization with veliparib in head and neck carcinoma cell lines and lung cancer xenograft models; or with niraparib in neuroblastoma cell lines, and whole brain radiation in cases of brain metastases [153] (Fig. 3b). In addition, Table 3 compiles various drug combinations with Olaparib (Table 3a) and Veliparib (Table 3b) which are being currently extensively used in various cancers along with its side effects.

The transcriptional role of PARP-1 in cancer includes chromatin modulation of tumour suppressor and oncogene function, regulation of the metastatic processes, alteration of cell survival and adaptation. For example, in liver cancer, ATPases activity of ALC1 (amplified in liver cancer 1) was found to be dependent upon both PARP-1 and NAD^{+}.[154] Furthermore, various tumour cell lines exhibited overexpression of PARP-1 with malignancy progression.[155] One of the recent studies indicated that following irradiation, PARP-1 activation plays a critical role in prostate cancer cell lines (LNCaP and DU145).[156]

PARP-1 is also thought to be an important modulator of tumour suppressor gene, p53.[157] In addition, PARP-1 is known to regulate organ site-specific tumour suppressors as explained by tumour

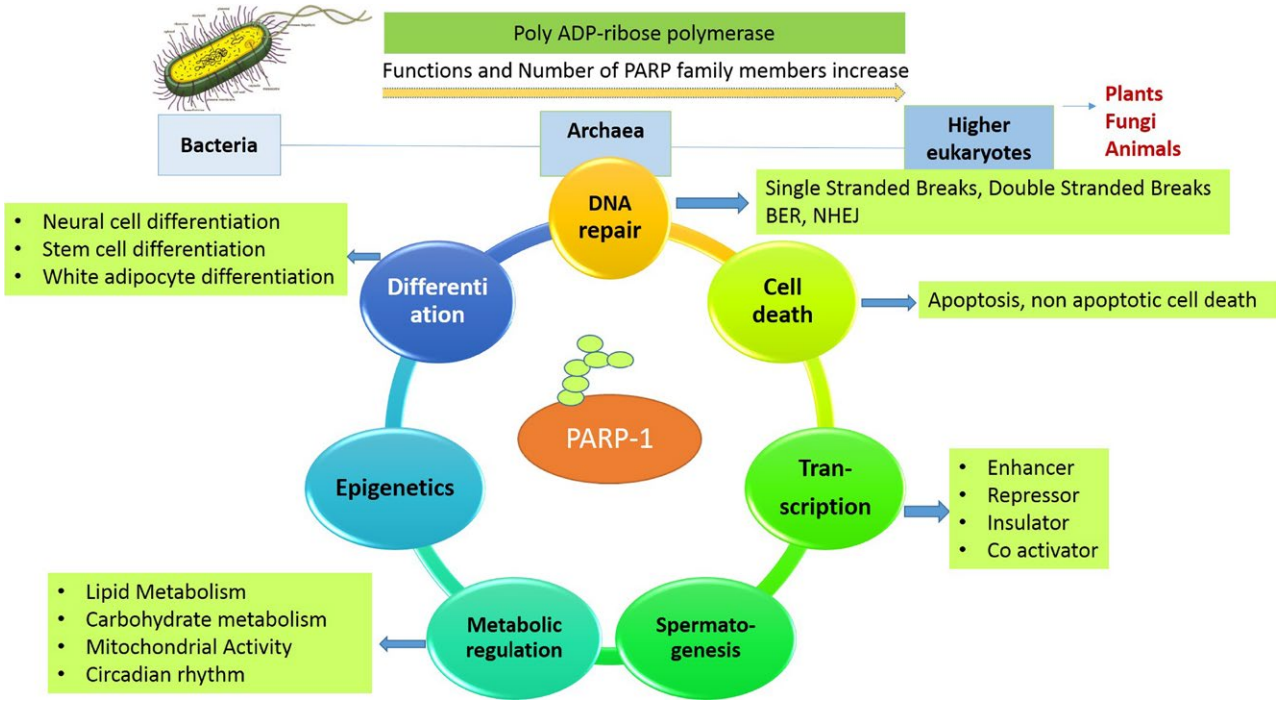

FIGURE 4 PARP-multifunctional protein. Poly ADP-ribose polymerase family of proteins are detected from prokaryotes to eukaryotes. The number of PARP family members and their involvement in various cellular processes increases with the complexity of the organism. PARP-1, the most studied PARP family member is involved a wide range of processes like DNA repair, cell death, transcription, spermatogenesis, metabolic regulation, epigenetics and differentiation

suppressor gene, APC (adenomatous polyposis coli). The loss of this gene was associated with sporadic colorectal cancer (CRC). Collective reports suggest that PARP-1 controls activity of T-cell factor (TCF)/lymphoid enhancer factor (LEF), i.e. TCF/LEF complex in CRC with higher expression levels of PARP-1.[158,159] In addition, Schiewer et al. [160] showed that PARP-1 controls androgen receptor (AR) association and functions with chromatin using in vitro and in vivo systems. In particular, reduction in AR activity was correlated with significant anti-tumour response to PARP-1 inhibition, indicating the dependence of prostate cancer on PARP-1 activity.[160] Thus, these studies suggest that inhibition of PARP-1 has potential as a cancer therapeutic through at least two mechanisms: (1) by potentiating chemotherapeutic agents that damage DNA and increasing tumour sensitivity; and (2) by inducing "synthetic lethality" in cells that are highly dependent on PARP-1, due to deficiency in homologous recombination such as BRCA1 mutants.

4.3.10 | Clinical implications of PARP-1 in other diseases

Dysfunctional PARP-1 has been linked to the onset and progression of myriad of diseases including cancer, ageing, diabetes, neurological diseases, etc. Several evidences point out the role of PARP-1 in cancer. In addition, PARP-1 has also been associated in neuronal pathology. PARP-1 inhibition has been proven to play a protective role in Parkinsons and Alzheimer's disease.[161] Moroni et al. also illustrated PARP-1 inhibitor HYDAMTIQ to be very effective in conferring neuroprotection post stroke.[162] In addition, PARP-1 activation plays a role in diabetic nephropathy, neuropathy and retinopathy. Studies in experimental models reflect the role of PARP-1 in inflammatory responses by promoting inflammation-relevant gene expression. Moreover, activation of NF-κB, AP-1 and heat shock factor protein-1 transcription factors, classically known to signal inflammatory gene expression are mediated by PARP-1.[163,164] PARP-1 also controls immunosuppressive function of regulatory T cells by destabilizing Foxp3.[165] Also, an increase in Foxp3^{+}T regulatory cells has been observed in PARP-1 deficiency.[166] PARP-1 has thus emerged as a very important therapeutic target not only in cancer but also in several other diseases which can be further probed for its therapeutic potential.

5 | CONCLUSION

The current research in PARP-1 biology unravels the role of PARP-1 beyond DNA repair and its involvement in several biological/cellular processes, such as epigenetics, transcriptional regulation, spermatogenesis, differentiation, etc. (Fig. 4). The role of PARP-1 as a transcriptional regulator has shed light on the broader aspect of PARP-1 in the cell. Recent studies have also highlighted the multifaceted role of PARP-1 in transcriptional regulation and provided new insights into how PARP-1 plays a very important role in signalling pathways in the cell. In addition, PARP-1's potential in therapeutics for diverse disease conditions require more animal-based clinical studies. Much work needs to be done to understand how PARP-1 works in conjunction with the other PARP family members. Moreover, PARP-1 inhibitors have been a promising therapeutic for a wide range of pathological conditions. Inhibiting PARP activity uncovers potential of PARP inhibitors as promising candidates for cancer therapy, particularly in BRCA1/2-mutated cancers, alone or in combination with cytotoxic drugs. p53-deficient breast cancer cells treated with a PARP inhibitor happen to lose resistance to an apoptosis promoting, clinically active anti-tumour agent called doxorubicin. However, these PARP inhibitors have several side effects that are toxic to the cell as the reports clearly show PARP-1's role in physiological conditions. Hence, to harness the therapeutic potential of PARP-1, studies are required to find out new inhibitors with least side effects. Thus, PARP-1 has now opened new avenues for researchers to understand PARP-1's multifunctional role in the cell which would eventually aid to further expand the utility of PARP family and its inhibition in therapeutics.

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